FORM PTO-1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 146.1307

U.S. APPLICATION NO (If known, see 37 CFR 1.5): 09/202217

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR97/01023	June 10, 1997	June 11, 1996

TITLE OF INVENTION: NEW DEVICES INTENDED FOR THE TRANSDERMIC ADMINISTRATION OF TRIMEGESTONE, THEIR PREPARATION PROCESS AND THEIR USE AS MEDICAMENTS

APPLICANT(S) FOR DO/EO/US: Jean-Luc DUBOIS

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). Unexecuted
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: Replacement pages 32-40 and Replacement Figures 1-5 (5 sheets) of International Application; Replacement page 33 and Replacement Figures 1-5 (5 sheets) of English Translation; International Preliminary Examination Report in French; PCT/IB/306

U.S. APPLICATION NO (If known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
	PCT/FR97/01023	146.1307

17. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO..... $830.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... $640.00 No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))..$710.00 Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37CFR 1.445(a)(2)) paid to USPTO..... $950.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... $90.00	$970.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	32 -20 =	12	X $ 18	$ 216.00	
Independent Claims	-3 =		X $74.00	$	
Multiple dependent claims(s) (if applicable)			+ $230.00	$	
TOTAL OF ABOVE CALCULATIONS =				$1186.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	-
SUBTOTAL =				$1186.00	
Processing fee of $130.00 for furnishing the English translation later the [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$	
TOTAL NATIONAL FEE =				$1186.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property			+	$	
TOTAL FEES ENCLOSED =				$ 1186.00	
				Amount to be: refunded	$
				charged	$

a. [X] A check in the amount of $1186.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [XX] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2275. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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SIGNATURE

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19,683
REGISTRATION NUMBER

Form PTO-1390 (REV 5-93)

Our Ref.: 146.1307

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
PCT/FR97/01023
Jean-Luc DUBOIS
Serial No.:
Filed: Concurrently Herewith
For: NEW DEVICES...AS MEDICAMENTS

PCT Date: June 10, 1997

600 Third Avenue
New York, NY 10016

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE CLAIMS:

Claim 11, line 1, cancel "or 10".

Claim 12, line 5, cancel "or 2".

Claim 13, line 2, cancel "any one of claims 3 to 5" and insert --claim 3--.

Claim 14, line 2, cancel "one of claims 6 to 8" and insert --claim 6--.

Claim 15, line 2, cancel "any one of claims 9 to 11" and insert --claim 9--.

Claim 21, line 1, cancel "or 20".

Claim 23, line 1, cancel "or 22".

line 4, cancel "or 8".

Claim 26, line 2, cancel "or 13".

Claim 27, line 2, cancel "or 13".

Claim 28, line 2, cancel "or 14".

Claim 29, line 2, cancel "or 15".

Claim 31, line 1, cancel "any one of claims 12 to 16", and insert --claim 12--.

REMARKS

The amendment is submitted to conform the claim dependency to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS

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CAM:sd
Enclosure: Return Receipt Postcard

New devices intended for the transdermic administration of Trimegestone, their preparation process and their use as medicaments.

The present invention relates to new devices intended for the administration by transdermic route of trimegestone and their preparation process.

Transdermic systems delivering a progestomimetic are of great therapeutic interest.

Indeed, progestomimetic steroids are active ingredients which must be administered over long periods of time.

The delay esters of these steroids or galenic forms offering controlled release such as implants or microspheres are used therapeutically but often present the disadvantage of not being very easy to use. Moreover, they do not allow a rapid interruption of treatment if necessary.

A transdermic system has the advantage that it can be used for long-term treatment, while limiting overdoses. Using the transdermic route can also avoid undesirable effects such as overloading the liver.

The Applicant has thus come to study a new pharmaceutical compound which can be administered by transdermic route, containing a progestomimetic known under the name of Trimegestone (17alpha-methyl-17beta-(2-hydroxy-1-oxo-propyl)-estra-4,9-dien-3-one (21S)):

1 - which can contain the Trimegestone under good conditions of stability, in particular during storage,

2 - which allows administration of the Trimegestone at a transcutaneous flow of between 0.1 and 3 $\mu g.cm^{-2}.h^{-1}$,

3 - which allows delivery of the necessary dose of the active ingredient while maintaining a size (surface area) which is more acceptable than patches of the prior art,

4 - which has a simple and inexpensive manufacturing process

5 - which allows adhesion compatible with the necessary duration in particular for hormone replacement treatment for the menopause, i.e. for 3 to 7 days,

6 - which offers a grammage appropriate for the flow and adhesion criteria.

A subject of the invention is thus an adhesive polymer matrix applied to a device intended for the transdermic administration of a progestomimetic characterized in that said matrix contains one or more of the following successive layers:

- optionally a layer (1) known as an anchor layer constituted by a silicone polymer,
- a layer (2), constituted by a silicone polymer loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives, and optionally a plasticizer,
- optionally a layer (3) known as an adhesion layer, constituted by a silicone polymer.

Trimegestone is a powerful progestomimetic described in European Patent EP-0007823.

By pharmaceutically acceptable derivatives is meant the esters in position 21 of Trimegestone, the remainder of the ester group containing from 1 to 12 carbon atoms. In particular, this is the 17beta-(2-acetoxy-1-oxo propyl) estra-4,9-dien-3-one (21S) derivative. It may also be the following 2-acyloxy groups: isopropionyloxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, oxalyloxy, succinyloxy, pivaloyloxy, undecanoyloxy, benzoyloxy. These esters are in particular prepared by the action of aliphatic or aromatic carboxylic acids or anhydrides containing from 1 to 12 carbon atoms on the Trimegestone.

The esters of Trimegestone, the ester remainder of which contains 1 carbon atom or 3 to 12 carbon atoms, are also a subject of the present invention.

Among the many polymers known to a man skilled in the art, capable of containing a progestomimetic such as Trimegestone, the Applicant has determined that only one silicone polymer is able to meet the required conditions of stability, flow and adhesion.

By silicone polymer is meant a network of polydimethylsiloxane (PDMS) chains.

Two types of polymer can be used, one with a strong instant adhesive power, and in particular BIO-PSA® 7-4301,

the other with a medium instant adhesive power and in particular BIO-PSA® 7-3045, 7-4201 or 7-4202. (Dow Corning Health Care Centre Europe). The silicone polymer takes the form of a limpid solution in an organic solvent which is volatile at low temperatures such as hexane, heptane, ethyl acetate or tetrahydrofurane.

These polymers are amino-resistant and do not present any acid silanol groups.

Adhesive power is characterized by peeling force and adhesion force: this adhesive force increases on passing from low instant adhesive power to medium instant adhesive power. The parameter used to modulate this physical characteristic is the silicone polymer/resin ratio. By medium adhesive power is meant a ratio of 40/60. By strong adhesive power is meant a ratio of 45/55.

The quantity of Trimegestone incorporated in a polymer matrix as defined previously is between 1% w/w and 10% w/w. This percentage corresponds to the quantity of active ingredient expressed as a ratio of the dry weight of the mixture after evaporation of the solvent. The Trimegestone is then in a state of suspension within the silicone matrix.

The purpose of plasticizers is to increase the instant adhesion value. Oils such as silicone fluid or Cetiols such as Cetiol® S (dioctylcyclohexane) are used. More particularly, this will be high viscosity silicone fluid. This will be polymerised dimethylsiloxane and quite particularly DOW Corning's 7-9120 silicone fluid (12000 cSt). The quantity of plasticizer can vary from 1 to 10% w/w. The preferred choice will be from 1 to 3% w/w of plasticizer.

This silicone matrix offers a number of advantages:

- No absorption promoter,
- Trimegestone is chemically well stabilised in the silicone polymer,
- Flow and adhesion levels are compatible with therapeutic treatment,
- Compared with reservoir systems, the matrix system offers the advantage that it entails no risk of breaking a membrane, which could lead to an overdose of the active ingredient.

- Trimegestone is not affected when the manufacturing process is implemented although it is unstable to humidity and temperature.

The patches containing Trimegestone as described previously thus allow a distribution of the active ingredient that is spread over time. The concentration is stable in time, without any peaks (cf. pharmacodynamic tests).

More particularly, a subject of the invention is three types of matrix:

1 - a single-layer matrix,

2 - a two-layer matrix,

3 - a three-layer matrix, as described below.

1 - Single-layer matrix

A more particular subject of the invention is an adhesive polymer matrix applied to a device intended for the transdermic administration of a progestomimetic as defined previously characterized in that said matrix contains a single layer (2) constituted by a silicone polymer loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives and optionally a plasticizer.

More particularly, the preferred choice will then be the commercial adhesive silicone polymer having a strong instant adhesive power. The preferred choice will then be BIO-PSA® with a strong instant adhesive power, and in particular BIO-PSA® 7-4301.

It is unnecessary to use any absorption promoter.

A quite particular subject of the invention is the previous single-layer matrix, characterized in that it is constituted by 80 to 99% w/w of silicone polymer having a strong adhesive power loaded with 1 to 10% w/w of Trimegestone and/or one or more pharmaceutically acceptable derivatives and 0 to 10% w/w of silicone fluid or Cetiol® S,

A quite particular subject of the invention is the previous single-layer matrix, characterized in that it is constituted by 96% w/w of BIO-PSA® silicone polymer having a strong adhesive power loaded with 3% w/w of Trimegestone and 1% w/w of silicone fluid.

2 - Two-layer matrix

A more particular subject of the invention is also an adhesive polymer matrix applied to a device intended for the transdermic administration of a progestomimetic characterized in that said matrix contains two successive layers:

a) a first layer (2), comprising a silicone polymer loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives,

b) the second layer, the adhesion layer which is in contact with the skin, also constituted by a silicone polymer.

As regards the loaded layer and the adhesion layer, the more particularly preferred choice will be the commercial adhesive silicone polymer having a strong instant adhesive power. The preferred choice will then be BIO-PSA® with a strong instant adhesive power, and in particular BIO-PSA® 7-4301.

The addition of an adhesion layer, which must be on the skin, in the two-layer formula has allowed an increase in adhesion without however significantly modifying the flow. It is thus unnecessary to use an absorption promoter.

A quite particular subject of the invention is also more particularly the previous two-layer matrix characterized in that

a) the first layer is constituted by 90 to 99% w/w of a silicone polymer having a strong adhesive power loaded with 1 to 10% w/w of Trimegestone and/or one or more pharmaceutically acceptable derivatives,

b) the second layer is also constituted by a silicone polymer with a strong adhesive power.

A quite particular subject of the invention is also the previous two-layer matrix characterized in that

a) the first layer is constituted by 97% w/w of a BIO-PSA® silicone polymer with a strong adhesive power, loaded with 3% w/w of Trimegestone,

b) the second layer is also constituted by a BIO-PSA® silicone polymer with a strong instant adhesive power.

3 - Three-layer matrix

A more particular subject of the invention is also an adhesive polymer matrix applied to a device intended for the transdermic administration of a progestomimetic as defined previously characterised in that said matrix contains three successive layers:

- a first layer (1) known as an anchor layer constituted by a silicone polymer,

b) a second layer (2), constituted by a silicone polymer loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives,

c) and a third layer (3), the adhesion layer which is in contact with the skin, also constituted by a silicone polymer.

The addition of an anchor layer and an adhesion layer has allowed an increase in adhesion without, however, significantly modifying the flow. It is thus unnecessary to use any absorption promoter.

As regards the adhesion layer, the more particularly preferred choice will be the commercial adhesive silicone polymer having a strong instant adhesive power. The choice will then be BIO-PSA® with a strong instant adhesive power, and in particular BIO-PSA® 7-4301.

As regards the anchor layer and the loaded layer, the more particularly preferred choice will be the silicone polymer with a medium instant adhesive power and in particular BIO-PSA® 7-3045, 7-4201 or 7-4202.

A quite particular subject of the invention is also the previous three-layer matrix characterized in that

- the first layer is constituted by a silicone polymer having a medium adhesive power,
- the second layer is constituted by 90 to 99% w/w of a silicone polymer having a strong adhesive power loaded with 1 to 10% w/w of Trimegestone and/or one or more pharmaceutically acceptable derivatives,
- the third layer is constituted by a silicone polymer with a strong adhesive power.

A quite particular subject of the invention is also the

previous three-layer matrix characterized in that
- the first layer is constituted by a BIO-PSA® silicone polymer having a medium instant adhesive power,
- the second layer is constituted by 91% w/w of BIO-PSA® silicone polymer having a medium instant adhesive power loaded with 9% w/w of Trimegestone,
- the third layer is constituted by a BIO-PSA® silicone polymer with a strong instant adhesive power.

A subject of the invention is also a device intended for the transdermic administration of a progestomimetic characterized in that it is successively constituted by:
- a protective film (a),
- a matrix loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives as defined previously,
- a peel-off protective film (b).

The protective films used are supports on which the different layers constituting the patch are coated, in order to obtain an indissociable system. They can be opaque if the active ingredient is photosensitive.

Among the protective films, Scotchpak® 1109 is preferably chosen, as this is a skin-coloured, occlusive and flexible film, or Scotchpak® 1006 (3M Health Care Limited). Scotchpak® 1006 is constituted by 4 layers:
a) a skin-coloured pigmented layer
b) an aluminium layer
c) a polyethylene terephthalate layer
d) a medium-density polyethylene and ethylene acetate layer.

Among the other protective films known to a man skilled in the art which can apply to the present invention, there can also be mentioned the Hostaphan® RN series (RN23, RN25, RN75 or RE75).

The peel-off protective films used are films intended to protect the adhesive side to be stuck on the skin from the transdermic system after manufacture and during storage.

Among the peel-off protective films known to a man skilled in the art, the preferred choice will be a polyester film one face of which is treated with fluorocarbons such as

Scotchpak® 1022 (3M Health Care Limited) or a transparent polyester film Silox® B5Y/O (Akrosil™) one face of which has been treated against adhesion with Dow-Corning Bio-release silicones.

More particularly, a subject of the invention is the devices as described previously, successively containing (Figure 1):

- a protective film (a),
- a single-layer matrix (2) as described previously,
- a peel-off protective film (b).

More particularly, a subject of the invention is devices as described previously, successively containing (Figure 2):

- a protective film (a),
- a two-layer matrix ((2) and (3)) as described previously,
- a peel-off protective film (b).

More particularly, a subject of the invention is the devices as described previously, successively containing (Figure 3):

- a protective film (a),
- a three-layer matrix ((1), (2) and (3)) as described previously,
- a peel-off protective film (b).

The protective films are preferably opaque Scotchpak® 1006 protective films and the peel-off protective films are preferably Scotchpak® 1022 peel-off protective films.

These transdermic systems allow delivery of the Trimegestone at a transcutaneous flow ex vivo on human skin of between 0.1 and 3 $\mu g.cm^{-2}.h^{-1}$,

The devices as described previously can be of any shape: round, oval, rectangular or square. They have a surface area of between 5 and 50 cm^2.

The Trimegestone can be combined with an oestrogen.

Therefore a subject of the invention is also a device intended for the transdermic administration of a progestomimetic characterized in that it also contains a matrix loaded with oestrogen, this device being constituted by two compartments (A) and (B).

Among the preferred oestrogens there can be mentioned

17-beta-oestradiol, the esters of 17-beta-oestradiol such as oestradiol valerate, cyprionate, decanoate and acetate, ethynyl oestradiol, oestrone, an oestrogen of "equine origin" such as Premarin® or a combination of these compounds.

More particularly, a subject of the invention is the device as described previously characterized in that the oestrogen compound is oestradiol.

More particularly, a subject of the invention is the device as described previously characterized in that the two compartments (A) and (B)

- are supported by the same peel-off protective film (b),
- and are separated by an empty space or a barrier of 1 to 10 mm,
- compartment (A) containing a silicone polymer matrix loaded with trimegestone and/or one or more pharmaceutically acceptable derivatives as described previously,
- compartment (B) containing an adhesive polymer matrix loaded with oestrogen,
- each of these matrices being respectively covered with a protective film (a) and (a') which are identical or different (Figure 4).

Compartment (A) has a surface area of between 5 and 50 cm^2 and compartment (B) has a surface area of between 5 and 50 cm^2.

Therefore the peel-off protective film supports two separate compartments (A) and (B) respectively containing Trimegestone and an oestrogen compound.

Once this peel-off protective film has been removed, two separate patches are obtained which are applied to the skin or mucous membranes so that administration of the Trimegestone and the oestrogen compound is simultaneous and separate. There can also be one or more fixing means between the two compartments (A) and (B) in order that the two patches remain joined once the peel-off protective film is removed.

The polymer matrix containing the oestrogen compound is selected from the polymers which are available commercially and/or known to a man skilled in the art. These are in

particular polymers or copolymers comprising a network of polyisobutylene or polyacrylic chains, ethylene and vinyl acetate (EVA) copolymers or also silicone polymers. If appropriate, a hydrophilic polymer and/or absorbent promoter and/or plasticizer and/or other additives known to a man skilled in the art which might improve flow, adhesion and transdermic system stability criteria can be added to these copolymers.

This matrix can be single or multi-layered. A reservoir system can also be used.

The empty space used to separate the two compartments can be from 1 to 10 mm. The preferred size is from 2 to 4 mm.

By "barrier" is meant a physical separator constituted by a suitable material. Its width is defined in terms of its ability to stop distribution and by the manufacturing process. Its width can be between 1 and 10 mm. It will preferably be between 1 and 3 mm wide.

When the oestrogen compound is oestradiol, the loaded matrix will preferably be a mono-layer matrix comprising a 2-ethylhexyl acrylate and vinyl acetate mixture loaded with oestradiol, to which a hydrophilic polymer may optionally be added. More particularly, this will be the Gelva® 737 copolymer containing 72% of 2-ethylhexyacrylate and 28% of vinylacetate. The preferred hydrophilic polymer is polyvinylpyrrolidone. More particularly, this will be Kollidon® 30 or 90F.

The quantity of oestradiol incorporated in a polymer matrix as defined previously is preferably between 1% w/w and 10% w/w.

More particularly, a subject of the invention is devices as described previously, presenting the following characteristics:

BIPATCH 1 comprising

- a peel-off protective film (b) supporting two compartments (A) and (B), separated by an empty space or a barrier of 1 to 10 mm,
- compartment (A) containing a single-layer matrix, covered

by a protective film (a), and constituted by a silicone polymer loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives, and optionally a plasticizer,

- and compartment (B) containing a single-layer matrix, covered with a protective film (a'), constituted by a 2-ethylhexyl acrylate and vinyl acetate copolymer, loaded with oestradiol and optionally a hydrophilic polymer.

BIPATCH 2 comprising

- a peel-off protective film (b) supporting two compartments (A) and (B), separated by an empty space or a barrier of 1 to 10 mm,
- compartment (A) containing a two-layer matrix covered by a protective film (a),

a) the first layer is constituted by a silicone polymer loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives,

b) the second layer, the layer that adheres to the skin, also being constituted by a silicone polymer.

- and compartment (B) containing a single-layer matrix, covered with a protective film (a'), constituted by a 2-ethylhexyl acrylate and vinyl acetate copolymer, loaded with oestradiol and optionally a hydrophilic polymer.

More particularly, a subject of the invention is devices as described previously, containing:

BIPATCH 1a comprising

- a peel-off protective film (b) supporting two compartments (A) and (B), separated by an empty space or a barrier of 1 to 10 mm,
- compartment (A) containing a single-layer matrix, covered by an opaque protective film (a) and constituted by 80 to 99% w/w of silicone polymer having a strong adhesive power loaded with 1 to 10% w/w of Trimegestone and/or one or more pharmaceutically acceptable derivatives and with 0 to 10% w/w of silicone fluid or Cetiol S,
- compartment (B), containing a single-layer matrix covered by a protective film (a') and constituted by 60 to 99% w/w of Gelva® 737 loaded with 1 to 10% w/w of oestradiol and 0 to

30% w/w of Kollidon®.

BIPATCH 2a comprising

- a peel-off protective film (b) supporting two compartments (A) and (B), separated by an empty space or a barrier of 1 to 10 mm,
- compartment (A) containing a two-layer matrix covered by a protective film (a),

a) the first layer is constituted by 90 to 99% w/w of a silicone polymer having a strong adhesive power loaded with 1 to 10% w/w of Trimegestone and/or one or more pharmaceutically acceptable derivatives,

b) the second layer, the layer that adheres to the skin, also being constituted by a silicone polymer with a strong adhesive power,

- and compartment (B), containing a single-layer matrix covered by a protective film (a') and constituted by 60 to 99% w/w of Gelva® 737 loaded with 1 to 10% w/w of oestradiol and 0 to 30% w/w of Kollidon®.

This "bipatch":

- allows the combination in a single entity of the Trimegestone and an oestrogen compound to be administered simultaneously, separately and over a period of time for hormone replacement treatment relating to the menopause and in particular the prevention or treatment of osteoporosis.
- resolve problems of differences in stability for active ingredients in polymers used for loaded layers: Trimegestone is not stable in the matrix used for oestradiol,
- allows the administration of each active ingredient under optimum conditions in order to obtain a pharmaceutically acceptable transcutaneous flow and avoids all interaction between a compound and the matrix of the other compound,
- allows conformation with the stipulated requirements regarding doses and the day of administration of each active ingredient (predosage), while avoiding the purchase, and the manipulation of two individual patches.

In the context of an oestrogen-progestogen combination, the last point is particularly important for hormone replacement treatment relating to the menopause and in

particular the prevention or the treatment of osteoporosis as well as for contraceptive treatment.

It also offers the following advantage: by applying two separate matrices on the same peel-off protective film, it is easy to:

- separately optimise the formulations containing the active ingredients (selection of the support polymer, selection of an absorption promoter, selection of the hydrophilic polymer, selection of a plasticizer, optimisation of grammage), as a function of the required adhesion and flow criteria,
- separately optimise the concentrations of the active ingredients as a function of required stability and transcutaneous flow criteria and prescribed doses,
- obtain compartments of identical or different sizes, by a simple manufacturing process.

A subject of the invention is also a device ("combipatch") constituted successively by the following elements:

a protective film (a),

a compartment (B) constituted by an adhesive polymer matrix loaded with an oestrogen such as oestradiol,

a polyester film (c) having the same dimensions as compartment (A) and situated on top of it,

a compartment (A) constituted by silicone polymer matrix loaded with Trimegestone and/or with various pharmaceutically acceptable derivatives, as defined above, compartment (A) being smaller in size than compartment (B) for example half its size and preferably being centred in relation to compartment (B),

a peel-off protective film (b).

Compartment (A) is smaller in size than compartment (B) so that the matrix loaded with oestrogen situated above the matrix loaded with Trimegestone can also be in direct contact with the skin. The oestrogen compound will thus be diffused directly from this location. For example, compartment (A) may have a surface area of 15 cm^2 and compartment (B) may have a surface area of 30 cm^2 (see Figure 5).

As a matter of preference, compartment (A) is constituted by a two-layer or three-layer matrix as defined previously.

The "combipatch" having a two-layer matrix can for example be used for 4 days and the "combipatch" having a three-layer matrix can for example be used for 7 days.

The manufacturing technique for transdermic systems which are a subject of the invention is coating. The general principle is as follows:

A silicone polymer solution is mixed in an apolar organic solvent such as heptane with the active ingredient and any other additive, and a suspension or a solution of adhesive (2) is obtained which is spread (coating) on a peel-off protective film or a protective film. After optional pre-evaporation under a fume hood at ambient temperature, the film is dried at a temperature of between 40°C and 100°C until complete evaporation of the solvent. This type of operation is repeated in an appropriate order according to the number of layers required, then the transdermic system is cut into pastilles, called patches, the surface area of these patches being between 1 and 50 cm^2. By adhesive solution (1) or (3) is meant silicone polymer solutions in an apolar organic solvent such as heptane, not loaded with active ingredient.

The "single-layer" patch can be prepared as follows:

1 - a solution of adhesive layer (2) in heptane loaded with Trimegestone and optionally a plasticizer is first applied to a peel-off protective film (b) and then dried,

2 - the "adhesive layer (2)/peel-off protective film (b)" set is colaminated on the protective film (a),

3 - the transdermic systems are cut into pastilles with a surface area of between 5 cm^2 and 50 cm^2.

In this way the "bipatch" is obtained characterized in that it contains (Figure 1):

- a protective film (a)
- an adhesive layer (2) loaded with Trimegestone and optionally with a plasticizer,
- a peel-off protective film (b).

The manufacturing process can also be carried out as follows

1 - a solution of adhesive layer in heptane loaded with Trimegestone and optionally a plasticizer (2) is first applied to a protective film (a) and then dried,

2 - the "adhesive layer (2)/protective film (a)" set is colaminated on a peel-off protective film (b),

3 - the transdermic systems are cut into pastilles with a surface area of between 5 cm^2 and 50 cm^2.

The "two-layer" patch can be prepared as follows:

1 - there are first applied:

a) a solution of adhesive layer (3) in heptane to a peel-off protective film (b) and then dried,

b) a solution of adhesive layer (2) in heptane loaded with Trimegestone to a temporary peel-off protective film (b') and then dried,

2 - the "adhesive layer (2) loaded with Trimegestone/temporary peel-off protective film (b')" set is colaminated on the "adhesive layer (3)/peel-off protective film (b) set,

3 - the temporary protective film (b') is peeled away,

4 - the "adhesive layer (2)/adhesive layer (3)/peel-off protective film (b)" set is colaminated on a protective film (a),

5 - the transdermic systems are cut into pastilles with a surface area of between 5 cm^2 and 50 cm^2.

In this way the "bipatch" is obtained characterized in that it contains (Figure 2):

- a protective film (a),
- an adhesive layer loaded with Trimegestone (2),
- an adhesive layer between the loaded layer and the peel-off protective film (3),
- a peel-off protective film (b).

The "three-layer" patch can be prepared as follows:

1 -

a) a solution of adhesive layer (1) in heptane is first applied to a temporary peel-off protective film (b') and then dried,

b) a solution of adhesive layer (2) in heptane loaded with Trimegestone is first applied to a temporary peel-off protective film (b'') and then dried,

c) a solution of adhesive layer (3) in heptane is first applied to a peel-off protective film (b) and then dried,

2 - the "adhesive layer (1)/temporary peel-off protective film (b')" set is colaminated on a protective film (a),

3 - the temporary protective film (b') is peeled away,

4 - the "adhesive layer (2) loaded with Trimegestone/temporary adhesive layer (b'')" set is colaminated on the "adhesive layer (1)/protective film (a)" set,

5 - the temporary protective film (b'') is peeled away,

6 - in the final colamination operation, the "adhesive layer (3)/peel-off adhesive layer (b)" set is colaminated on the "loaded layer (2)/adhesive layer (1)/protective film (a)" set,

7 - the transdermic systems are cut into pastilles with a surface area of between 5 cm^2 and 50 cm^2.

In this way the patch is obtained characterized in that it contains (Figure 3):

- a peel-off protective film (b),
- an adhesive layer between the protective film and the loaded layer (3),
- an adhesive layer loaded with Trimegestone (2),
- an adhesive layer between the loaded layer and the protective film (anchor layer) (1),
- a protective film (a).

The "bipatch" device allowing the transdermic administration of Trimegestone combined with an oestrogen as described previously can be prepared as follows:

Stage I: for the manufacture of the patch corresponding to compartment (A)

1 - the silicone adhesive polymer layer loaded with Trimegestone and optionally one or more additives is coated on the protective film (a),

2 - the solvent is evaporated off until the "matrix loaded with Trimegestone (I)/protective film (a)" set corresponding

to compartment (A) is obtained,

3 - the "matrix loaded with Trimegestone/protective film (a)" set is colaminated on a peel-off protective film (b'),

4 - a patch of 5 to 50 cm² is cut out.

Stage II: for the manufacture of the patch corresponding to compartment (B)

1 - the adhesive polymer layer loaded with an oestrogen compound and optionally one or more additives such as a hydrophilic polymer, an absorption promoter or a plasticizer is coated on the protective film (a'),

2 - the solvent is evaporated off until the "matrix loaded with oestrogen/protective film (a')" set corresponding to compartment (B) is obtained,

3 - the "matrix loaded with oestrogen/protective film (a')" set is colaminated on a peel-off protective film (b'),

4 - a patch of 5 to 50 cm² is cut out.

Stage III: for the manufacture of the "bipatch"

1 - the peel-off protective film (b') is peeled from the patch obtained in Stage 1,

2 - the "matrix loaded with Trimegestone/protective film (a)" set is transferred onto a peel-off protective film (b),

3 - the peel-off protective film (b'') is peeled from the patch obtained in Stage 2,

4 - the "matrix loaded with oestrogen/protective film (a')" set is transferred onto the previous peel-off protective film (b), respecting a distance of 1 to 10 mm or after placing a barrier between compartments (A) and (B).

In this way the "bipatch" is obtained characterized in that it contains (Figure 4):

- a peel-off protective film (b),
- a compartment (A) constituted by a matrix loaded with trimegestone as defined previously and covered by a protective film (a)
- a compartment (B) constituted by a matrix loaded with an oestrogen compound and covered by a protective film (a'), the two compartments being separated from each other by an empty space or a barrier of 1 to 10 mm.

All these procedures can also apply to the esters of

Trimegestone as defined previously.

These different processes are in all cases less expensive than the manufacturing processes using reservoir systems. They are simple processes to implement and which require relatively short drying times. Preferably, drying is carried out at 60°C for 15 minutes.

Drying is carried out as a continuous industrial process. The manufacturing conditions are as follows: segment I: 35°C, segment II: 50°C, segment III: 60°C and segment IV: 80°C.

The manufacturing process for a single-layer patch is particularly simple as on the one hand there is only a single layer, then there is no loss of transfer film necessary during colamination operations and finally simplification of adjustments relating to a colamination. It is inexpensive for the reasons mentioned above, but also because it allows a high speed of manufacture and it requires less raw material (Trimegestone and excipients). The manufacturing process of a two-layer patch has the advantage relative to a single-layer of not requiring the provision of a plasticizer.

Trimegestone has a very good affinity vis-à-vis the progesterone receptor (6 to 7 times that of progesterone). Moreover, it has a very weak affinity vis-à-vis the androgen receptor and no affinity vis-à-vis the oestrogen receptor (<0.02). Studies in vivo have confirmed the studies in vitro. Trimegestone is a powerful progestomimetic devoid of mineralocorticoid, androgen, glucocorticoid, antiglucocorticoid and oestrogen activity. On the other hand it has an antimineralocorticoid and antiandrogen activity. Therefore, Trimegestone in the form of a patch is of great interest in therapeutics.

The patch containing Trimegestone according to the invention can be used in the treatment of gynaecological problems due to a luteal insufficiency:

- menstrual problems and/or problems relating to the menstrual cycle,
- dysmenorrhea,
- premenstrual syndrome,

- mastodynia, mastopathy,
- functional haemorrhages,
- menorrhagia of the fibroma,
- endometrial hyperplasia,
- premenopause problems,
- endometriosis
- menopause problems
- contraception,
- ovarian dystrophies due to inactivity of the ovaries,
- treatment of tumours and the uterus.

In combination with an oestrogen such as oestradiol, the progestational Trimegestone shows a strong anti-oestrogen activity at the level of the uterus while not showing any antioestrogen activity at the level of the bone structure. The oestrogen/Trimegestone combination according to the invention therefore finds a use in hormone replacement treatment related to the menopause and in particular in the prevention or treatment of osteoporosis.

Among the preferred oestrogens there can be mentioned 17-beta-oestrodiol, the esters of 17-beta-oestrodiol such as oestrodiol valerate, cyprionate, decanoate and acetate, ethynyl oestradiol, oestrone, oestrogen of "equine origin" such as Premarin(r) or a combination of these compounds.

As regards osteoporosis, it is a pathology which is characterized by a quantitative and qualitative reduction in bone matter, sufficient to lead to vertebral or peripheral fractures, in a spontaneous fashion or on occasions due to minimal traumas. Although this illness has many factors at its origin, it is the menopause, which in women, constitutes the dominating factor in bone loss or osteopenia.

This osteopenia manifests itself by a rarefaction and modification of the architecture of the spongy bone the consequence of which is to increase the fragility of the skeleton and the risk of fractures. Bone loss increases strongly after the menopause due to the suppression of ovarian function and reaches 3 to 5% per year before slowing down after 65 years of age.

For a therapeutic purpose, the post-menopause hormonal

deficiency can be compensated for by a replacement hormone therapy where oestrogen plays a major role in preserving the bone mass. But long-term oestrogenotherapy is sometimes accompanied by undesirable effects on the genital apparatus (endometrial hyperplasia, breast tumours ...), which constitutes a major drawback and limits its use. Consequently it is appropriate to combine with oestrogen, a progestational hormone which is capable of opposing the side effects of oestrogen on genital targets whilst maintaining its beneficial action on bone. Combinations of this type are already known and are described for example in the following Patents or Patent Applications EP-0136011, US5208225, US5108995, EP-474374, DE4019670. However, they have a significant drawback due to the multiplicity of activities associated with the progestational hormones used in the combinations and in particular their androgen effects.

The combination does not have this drawback. In fact, trimegestone which belongs to the norpregnane class of progestational hormones, is practically devoid of any androgen activity, which leads to a good metabolic tolerance.

The oestrogen/Trimegestone combination according to the invention also finds a use as a contraceptive. The oestrogen will then quite particularly be ethynyloestradiol.

Therefore a subject of the invention is the device as described previously for its use, as a delivery process, either of Trimegestone and/or one or more pharmaceutically acceptable derivatives i.e. Trimegestone combined with an oestrogen, to a patient by the application of the matrix or matrices of the device on the skin or mucous membranes of said patient.

The examples of treatment below illustrate the invention without however limiting it.

1) Trimegestone alone

Treatment a

A first patch can be applied from the 16th to the 18th day of the cycle, a second patch from the 19th to the 21st day of the cycle and a third patch from the 22nd to the 25th

day of the cycle, i.e. 10 days per cycle.

Treatment b

A first patch can be applied from the 5th to the 8th day of the cycle, a second patch from the 9th to the 12th day of the cycle, a third patch from the 13th to the 16th day of the cycle, a fourth patch from the 17th to the 21st day of the cycle and a fifth patch from the 22nd to the 25th day of the cycle, i.e. 21 days per cycle.

Continuous Trimegestone treatment can also be used.

2) Trimegestone combined with oestradiol

In the context of hormone replacement treatment for the menopause and in particular in the prevention or treatment of osteoporosis. The oestradiol can be in tablet form or in the form of a patch.

Sequential administration of Trimegestone and continuous administration of oestradiol:

Treatment a

Continuous administration of the oestradiol (28-day cycles with no break between cycles) at a dose of 25 to 200 μg per day and of Trimegestone for the last 14 days of each 28-day cycle at a dose of 0.05 to 2.5 mg per day.

Treatment b

Administration of oestradiol 28 days per month at a dose of 25 to 200 μg per day and of Trimegestone for the last 14 days of the administration of oestradiol, at a dose of 0.05 to 2.5 mg per day. The treatment is stopped for 2 to 3 days per month at the end of each 28-day cycle.

Treatment c

Administration of the oestradiol 28 days per month at a dose of 25 to 200 μg per day and of Trimegestone for the first 14 days of the administration of oestradiol, at a dose of 0.05 to 2.5 mg per day. The treatment is administered either without a break between each 28-day cycle or with a break of 2 to 3 days per month at the end of each cycle.

Treatment d

Administration of the oestradiol 25 days per month at a dose of 25 to 200 μg per day and of Trimegestone at a dose of 0.05 to 2.5 mg per day for the last 11 to 14 days of administration of the oestradiol. The treatment is stopped for 5 to 6 days at the end of the 25-day cycle.

Continuous administration of Trimegestone and oestradiol

Continuous administration of the oestradiol at a dose of 25 to 200 μg per day and of the trimegestone patch at a dose of 0.05 to 2.5 mg per day. There is no break in treatment.

3) Trimegestone combined with ethynyloestradiol

In the context of use as a contraceptive.

The Trimegestone patch in combination with the ethynyloestradiol is administered continuously for 21 to 28 days per cycle. This treatment requires the successive application of 3 to 8 Trimegestone patches and the administration of ethynyl oestradiol for 21 to 28 days/cycle,

in particular in the form of a patch or tablets.

Examples of patches according to the invention are shown hereafter in the experimental part. The following examples illustrate the invention without however limiting it.

Example 1:

Single-layer patch containing Trimegestone

- A Scotchpak 1006 opaque protective film of 70 ± 2 μm thickness **(a)**,
- A layer of 94% w/w of BIO-PSA silicone polymer loaded with 3% w/w of Trimegestone and 1% w/w of silicone fluid, from 50 to 60 μm thick **(2)**,
- A Scotchpak 1022 peel-off protective film 70 ± 1 μm thick **(b)**.

This patch has a surface area of 20 cm² and delivers ex vivo 0.80 ± 0.54 $\mu g.h^{-1}.cm^{-2}$ of Trimegestone (see Figure 1). The following matrices have been prepared:

EXAMPLE 1a: (single-layer matrix)
Patch surface area 20cm², Grammage 60 g/m²

Components	% w/w	mg/patch
Trimegestone	3	3.6
BIO-PSA® 7-4301	96	115.2
Silicone fluid 7-9120	1	1.2
Total	100	120

EXAMPLE 1b: (single-layer matrix)
Patch surface area 20cm², Grammage 60 g/m²

Components	% w/w	mg/patch
Trimegestone	3	3.6
BIO-PSA® 7-4301	94	112.8
Silicone fluid 7-9120	3	3.6
Total	100	120

EXAMPLE 1c: (single-layer matrix)

Patch surface area 20cm², Grammage 60 g/m²

Components	% w/w	mg/patch
Trimegestone	3	3.6
BIO-PSA® 7-4301	92	110.4
Silicone fluid 7-9120	5	6.0
Total	100	120

Example 1d:

Patch surface area 20cm², Grammage 40 g/m²

Components	% w/w	mg/patch
Trimegestone	3	2.4
BIO-PSA® 7-4301	94	75.2
Silicone fluid 7-9120	3	2.4
Total	100	80

Example 1e:

Patch surface area 20cm², Grammage 80 g/m²

Components	% w/w	mg/patch
Trimegestone	3	4,8
BIO-PSA® 7-4301	94	150,4
Silicone fluid 7-9120	3	4,8
Total	100	160

EXAMPLE 1f: (single-layer matrix)

Patch surface area 20cm², Grammage 40 g/m²

Components	% w/w	mg/patch
Trimegestone	3	2.4
BIO-PSA® 7-4301	94	75.2
Cetiol® S	3	2.4
Total	100	80

EXAMPLE 1g: (single-layer matrix)

Patch surface area 20cm², Grammage 60 g/m²

Components	% w/w	mg/patch
Trimegestone	3	3.6
BIO-PSA® 7-4301	94	112.8
Cetiol® S	3	3.6
Total	100	120

EXAMPLE 1h: (single-layer matrix)

Patch surface area 20cm², Grammage 40 g/m²

Components	% w/w	mg/patch
Trimegestone	3	4.8
BIO-PSA® 7-4301	94	150.4
Cetiol® S	3	4.8
Total	100	160

Example 2:

Two-layer patch containing Trimegestone

- A Scotchpak 1006 opaque protective film of 70 ± 2 μm thickness **(a)**
- A layer of 97% w/w of BIO-PSA® silicone polymer having a strong adhesive power loaded with 3% w/w of Trimegestone, from 50 to 60 μm thick **(2)**,
- A BIO-PSA® adhesive layer having a strong instant adhesive power 65 μm thick **(3)**,
- A Scotchpak 1022 peel-off protective film 70 ± 1 μm thick **(b)**.

This patch has a surface area of 20cm² and delivers ex vivo 1.29 ± 0.45 $\mu g.h^{-1}.cm^{-2}$ of Trimegestone (see Figure 2). The following matrix was prepared:

Example 2a: (Two-layer matrix)

Patch surface area 20cm², Grammage 60 + 30 g/m²

Layer	Components	% w/w	mg/patch
Loaded layer	Trimegestone	3	3.6
	BIO-PSA® 7-4301	97	116.4
Layer adhering to the skin	BIO-PSA® 7-4301	100	60
	Total	-	180

Example 3:

The following "three-layer" patch was prepared:

This patch is constituted successively by the following layers:

- A Scotchpak 1006 opaque protective film of 70 ± 2 μm thickness **(a)**,
- A BIO-PSA® anchor layer having a medium instant adhesive power approximately 33 μm thick **(1)**,
- A layer of BIO-PSA® silicone polymer having a medium instant adhesive power (91% w/w) loaded with Trimegestone (9% w/w), from 50 to 60 μm thick **(2)**,
- A BIO-PSA® adhesive layer having a strong instant adhesive power approximately 65 μm thick **(3)**,
- A Scotchpak 1022 peel-off protective film 70 ± 1 μm thick **(b)**.

This patch has a surface area of 20cm² and delivers ex vivo 0.59 ± 0.33 $\mu g.h^{-1}.cm^{-2}$ of Trimegestone (see Figure 3). The following matrix was prepared:

Example 3a: (Three-layer matrix)

Patch surface area 20cm², Grammage 30.5 + 61.5 + 65 g/m²

Layer	Components	% w/w	mg/patch
Anchor layer	BIO-PSA® 7-4201	100	61
Loaded layer	Trimegestone BIO-PSA® 7-4201	9 91	11.07 111.93
Layer adhering to the skin	BIO-PSA® 7-4301	100	130
	Total	-	314

Example 4:

Patch containing Trimegestone combined with oestradiol

BIPATCH 1b (cf. Figure 4)

This bipatch has the following characteristics:

- a Scotchpak® 1022 peel-off protective film **(b)** approximately 70 μm thick, characterised in that it supports two compartments (A) and (B), separated from one another by an empty space of 2 to 4 mm
- compartment (A) contains a single-layer matrix, approximately 60 μm thick, covered by a Scotchpak® 1006 opaque protective film **(a)** approximately 70 μm thick and constituted by 96% w/w of BIO PSA® with a strong instant adhesive power loaded with 3% w/w of Trimegestone and 1% of silicone fluid (7-9120, 12000 cSt). The grammage is equal to 60 g/m².
- and compartment (B), containing a single-layer matrix, approximately 76 μm thick, covered by a Scotchpak® 1109 protective film **(a')** approximately 34 μm thick or Hostaphan® RN23 and constituted by 73% w/w of Gelva® 737 loaded with 2% w/w of oestradiol and 25% w/w of Kollidon® 90F. The grammage is equal to 80 g/m².

BIPATCH 2b

This bipatch has the following characteristics:

- a Scotchpak® 1022 peel-off protective film **(b)** characterised in that it supports two compartments (A) and

(B), separated from one another by an empty space of 2 to 4 mm

- compartment (A) containing a two-layer matrix covered with a Scotchpak® 1006 protective film **(a)**,

a) the first layer, loaded with 3% w/w of Trimegestone, being constituted by 97% w/w of a BIO PSA® silicone polymer having a strong instant adhesive power,

b) the second layer, the layer which adheres to the skin, constituted by a BIO PSA® silicone polymer with a strong adhesive power;

The total grammage is thus equal to 90 g/m²,

- and compartment (B) containing a single-layer matrix, covered by a Scotchpak® 1109 or Hostaphan® RN23 protective film **(a')** and constituted by 73% w/w of a Gelva® 737 layer loaded with 2% w/w of oestradiol and 25% w/w of Kollidon® 90F. The grammage is equal to 80 g/m².

Tests on the patch structure

The following patches were manufactured:

(I) A two-layer patch according to the invention containing 3% w/w of trimegestone, grammage of the loaded layer = 59.82 ± 1.77 g/m^2, grammage of the adhesive layer = 29.76 ± 3.67 g/m^2.

(II) A two-layer patch according to the invention containing 9% w/w of trimegestone, grammage of the loaded layer = 59.16 ± 2.77 g/m^2, grammage of the adhesive layer = 29.72 ± 3.31 g/m^2.

(III) A three-layer patch according to the invention containing 9% of trimegestone.

(IVa) A single-layer patch according to the invention containing 3% w/w of trimegestone, grammage = 61.1 ± 2.5g/m^2 (with a plasticizer: 1% w/w of silicone fluid).

(IVb) A single-layer patch according to the invention containing 3% w/w of trimegestone, grammage = 59.1 ± 0.9 g/m^2 (with a plasticizer: 1% w/w of Cetiol® S).

(IVc) A single-layer patch according to the invention

containing 3% w/w of trimegestone, grammage = 42.9 ± 3.0 g/m^2 (without a plasticizer).

(IVd) A single-layer patch according to the invention containing 3% w/w of trimegestone, grammage = 63.0 ± 3.83 g/m^2 (without a plasticizer).

Adhesion test:

Principle:

The instant adhesion strength is evaluated by placing a patch (surface area = 5 cm²) in contact with a steel surface (1 cm²) in known pressure conditions (compression force: 5 N, duration 60 s) and by measuring the energy required to separate the two surfaces. This measurement can be used to compare different formulae or to monitor the evolution of the adhesion over time.

Type of patch	Adhesion strength (N.m) x 10^{-3}
(I) two-layer 3%	56.4 ± 5.0
(II) two-layer 9 %	52.1 ± 4.2
(III) three-layer 9 %	49.4 ± 7.5
(IVa) single-layer 3% + 1% silicone fluid	33.5 ± 1.6
(IVb) single-layer 3% + 1% cetiol® S	31.1 ± 2.0
(IVc) single-layer 3 % (G≈40 g/m^2)	10.2 ± 1.7
(IVd) single-layer 3 % (G≈60 g/m^2)	35.6 ± 2.6

As regards the two-layer or three-layer patch, the active ingredient load contained in the loaded matrix does not modify the instant adhesion.

The presence of one or two adhesive layers on the loaded matrix significantly improves instant adhesion.

Transcutaneous flow ex vivo:

Principle:

A fragment of skin is set up on a cell for transcutaneous transfer, of Franz cell type. The transdermic system is stuck to the skin on the stratum corneum side. The active ingredient is released by the transdermic system, crosses the cutaneous barrier and is retrieved in the reception medium. The quantity of active ingredient is then dosed at regular time intervals.

Method:

The skin fragments originate from plastic surgery (breast or abdomen).

The skin is stored at 4°C in a survival liquid until it is cut up. After elimination of the sub-cutaneous fat, the skin is cut into a 300 μm thick sheet and stored at -30°C until used.

The skin is set up on the cell's reception compartment. The skin and the reception medium need to be left for approximately 15 hours to achieve equilibrium. The patch is then placed on the skin. The transcutaneous passage of the active ingredient is monitored by dosage of Trimegestone in the reception medium.

Type of patch	Flow (10^{-6}.g.h^{-1}.cm^{-2})
(I) two-layer 3%	1.29 ± 0.45
(II) two-layer 9 %	1.07 ± 0.75
(III) three-layer 9 %	0.59 ± 0.33
(IVa) single-layer 3% + 1% silicone fluid	0.80 ± 0.54
(IVb) single-layer 3 %+1 % cetiol®	0.68 ± 0.22
(IVc) single-layer 3 % (G≈40 g/m^2)	0.34 ± 0.24
(IVd) single-layer 3 % (G≈60 g/m^2)	1.42 ± 0.87

The presence of one or two additional layers does not significantly modify transcutaneous flow.

TEST ON THE AFFINITY OF TRIMEGESTONE VIS-A-VIS HORMONAL RECEPTORS

The affinity of Trimegestone was compared with other common progestomimetics: medroxypropgesterone (MPA), norethisterone (NE), Promegestone (PROM), gestodene (GEST) and levonorgestrel (LNOR). This affinity was tested on recombinant human hormonal receptors of progesterone (hPR), androgene (hAN), glucocorticoid (hGR) and oestrogen (hER). These receptors are obtained by overexpression in an insect cell - baculovirus SF9 system according to the methods described in particular in European Patent Application 0 629 635. The relative bond affinities (RBAs) are as follows:

Recept.	RBA					
	Trim.	MPA	NE	MPA	GEST	LNOR
hPR	588	298	134	469	868	323
hGR	13	58	1.4	8	38	7.5
hAN	2.5	36	55	3	71	58
hER	< 0.02	< 0.02	< 0.15	< 0.02	< 0.02	< 0.02

Pharmacokinetic study on Trimegestone

After application of the 4 three-layer 20 cm^2 patches (9% of Trimegestone) respectively for 4, 3, 4 and 3 days, the concentration of plasmatic Trimegestone remains stable until removal of the last patch with a mean value of 1.37 mg/ml. The flow of Trimegestone therefore has a mean value of 0.4 mg/day/patch. No changes in the plasmatic concentration levels of oestradiol and oestrone were observed. The plasmatic concentrations of FSH and LH for their part decrease by 31 and 38% respectively after 14 days of application (antigonadotropic effect of Trimegestone).

In conclusion, the Trimegestone patches according to the invention applied for 14 days (1 every three days) deliver a constant flow of Trimegestone with stable Trimegestone plasmatic concentrations and good local tolerance.

Figure No.1: Structure of single-layer patch ($20cm^2$)

(a) Protective film

(2) Loaded adhesive layer

(b) Peel-off protective film

Figure No.2: Structure of a two-layer patch ($20cm^2$)

(a) Protective film

(2) Loaded adhesive layer

(3) Adhesive layer

(b) Peel-off protective film

Figure No.3: Structure of a three-layer patch ($20cm^2$)

(a) Protective film

(1) Anchor layer

(2) Loaded adhesive matrix

(3) Adhesive layer

(b) Peel-off protective film

Figure No.4:

(B) Compartment containing oestradiol ($15cm^2$)

(A) Compartment containing Trimegestone ($20cm^2$)

(a') Protective film

(a) Protective film

(b) Peel-off protective film

Figure No. 5:

(B) Compartment containing oestradiol

(A) Compartment containing Trimegestone

(a) Protective film

(b) Peel-off protective film

(c) Polyester film

CLAIMS

1) Adhesive polymer matrix applied to a device intended for the transdermic administration of a progestomimetic characterised in that said matrix contains one or more of the following successive layers:

- optionally a layer (1), known as an anchor layer, constituted by a silicone polymer,
- a layer (2), constituted by a silicone polymer loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives, and optionally a plasticizer,
- optionally a layer (3), known as an adhesion layer, constituted by a silicone polymer.

2) Adhesive polymer matrix as defined in claim 1, characterized in that it contains a quantity of Trimegestone of between 1% w/w and 10% w/w.

3) Adhesive polymer matrix according to claim 1, characterized in that said matrix contains a single layer (2) constituted by a silicone polymer loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives and optionally a plasticizer.

4) Adhesive polymer matrix according to claim 3, characterized in that it is constituted by 80 to 99% w/w of silicone polymer having a strong adhesive power loaded with 1 to 10% w/w of Trimegestone and/or one or more pharmaceutically acceptable derivatives and with 0 to 10% w/w of silicone fluid or diocytylohexane.

5) Adhesive polymer matrix according to claim 4, characterized in that it is constituted by 96% w/w of silicone polymer having a strong instant adhesive power loaded with 3% w/w of Trimegestone and 1% w/w of silicone fluid.

6) Adhesive polymer matrix according to claim 1, characterized in that said matrix contains two successive layers:

a) a first layer (2), comprising a silicone polymer loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives,

b) a second layer (3), adhesion layer in contact with the

skin, also constituted by a silicone polymer.

7) Adhesive polymer matrix according to claim 6, characterized in that

a) the first layer is constituted by 90 to 99% w/w of a silicone polymer having a strong adhesive power loaded with 1 to 10% w/w of Trimegestone and/or one or more pharmaceutically acceptable derivatives,

b) the second layer is also constituted by a silicone polymer with a strong adhesive power.

8) Adhesive polymer matrix according to claim 7, characterized in that

a) the first layer is constituted by 97% w/w of a silicone polymer having a strong instant adhesive power, loaded with 3% w/w of Trimegestone,

b) the second layer is also constituted by a silicone polymer having a strong instant adhesive power.

9) Adhesive polymer matrix according to claim 1, characterized in that said matrix contains three successive layers:

- a first layer (1), known as an anchor layer, constituted by a silicone polymer,

b) a second layer (2), constituted by a silicone polymer loaded with Trimegestone and/or one or more pharmaceutically acceptable derivatives,

c) the third layer (3), the adhesion layer, which is in contact with the skin, also constituted by a silicone polymer.

10) Adhesive polymer matrix according to claim 9, characterized in that

- the first layer is constituted by a silicone polymer with a medium adhesive power,

- the second layer is constituted by 90 to 99% w/w of a silicone polymer having a strong adhesive power loaded with 1 to 10% w/w of Trimegestone and/or one or more pharmaceutically acceptable derivatives,

- the third layer is constituted by a silicone polymer with a strong adhesive power.

11) Adhesive polymer matrix according to claim 9 or 10,

characterized in that

- the first layer is constituted by a silicone polymer having a medium instant adhesive power,
- the second layer is constituted by 91% w/w of a silicone polymer having a medium instant adhesive power loaded with 9% w/w of Trimegestone,
- the third layer is constituted by a silicone polymer having a strong instant adhesive power.

12) Device intended for the transdermic administration of a progestomimetic, characterized in that it is successively constituted by:

- a protective film (a),
- a matrix as defined in claim 1 or 2,
- a peel-off protective film (b).

13) Device as defined in claim 12, characterized in that the matrix is as defined in any one of claims 3 to 5.

14) Device as defined in claim 12, characterized in that the matrix is as defined in one of claims 6 to 8.

15) Device as defined in claim 12, characterized in that the matrix is as defined in any one of claims 9 to 11.

16) Device as defined in claim 12, characterized in that it also contains a matrix loaded with oestrogen, said device being constituted by two compartments (A) and (B).

17) Device as defined in claim 16, characterized in that the oestrogen compound is chosen from 17-beta-oestradiol, the esters of 17-beta-oestradiol such as oestradiol valerate, cyprionate, decanoate and acetate, ethynyl oestradiol, oestrone and an oestrogen of "equine origin" such as Premarin® or a combination of these compounds.

18) Device as defined in claim 16, characterized in that the oestrogen compound is selected from 17-beta-oestradiol.

19) Device as defined in claim 16, characterized in that the two compartments (A) and (B)

- are supported by the same peel-off protective film (b),
- and are separated from each other by an empty space or a barrier of 1 to 10 mm,
- compartment (A) containing the silicone polymer matrix, loaded with trimegestone and/or one or more pharmaceutically

acceptable derivatives, as defined in any one of claims 1 to 11,

- compartment (B) containing an adhesive polymer matrix loaded with oestrogen,

- and each of these matrices being covered respectively by a protective film (a) and (a') which are identical or different.

20) Device according to claim 19, characterized in that:

- compartment (A) contains a single-layer matrix as defined in claim 3,

- and compartment (B) contains a single-layer matrix constituted by a 2-ethylhexyl acrylate and vinyl acetate copolymer, loaded with oestradiol, and optionally a hydrophilic polymer.

21) Device according to claim 19 or 20, characterized in that:

- compartment (A) contains a single-layer matrix, as defined in claim 4 or 5,

- and compartment (B) contains a single-layer matrix constituted by 60 to 99% of 2-ethylhexyl acrylate (72%) and vinyl acetate (28%) copolymer loaded with 1 to 10% w/w of oestradiol and 0 to 30% w/w of polyvinylpyrrolidone.

22) Device according to claim 19, characterized in that:

- compartment (A) contains a two-layer matrix as defined in claim 6,

- compartment (B) contains a single-layer matrix constituted by a 2-ethylhexyl acrylate and vinyl acetate copolymer, loaded with oestradiol and optionally a hydrophilic polymer.

23) Device according to claim 19 or 22, characterized in that:

- compartment (a) contains a two-layer matrix, as defined in claim 7 or 8,

- and compartment (B) contains a single-layer matrix constituted by 60 to 99% w/w of a 2-ethylhexyl acrylate (72%) and vinyl acetate (28%) copolymer loaded with 1 to 10% w/w of oestradiol and 0 to 30% w/w of polyvinylpyrrolidone.

24) Device according to claim 16, characterized in that it is constituted successively by the following elements:

a protective film (a),

a compartment (B) constituted by an adhesive polymer matrix loaded with an oestrogen such as oestradiol,

a polyester film (c) having the same dimensions as compartment (A) and located on top of it,

a compartment (A) constituted by silicone polymer matrix loaded with Trimegestone and/or with various pharmaceutically acceptable derivatives, as defined above, compartment (A) being smaller in size than compartment (B) for example half its size and preferably being centred in relation to compartment (B),

a peel-off protective film (b).

25) Device according to claim 24, characterized in that the matrix containing the Trimegestone is a two-layer matrix as defined in claim 6 or a three-layer matrix as defined in claim 9.

26) Manufacturing process for devices according to claim 12 or 13, characterized in that:

1 - a solution of adhesive layer (2) in heptane loaded with Trimegestone and optionally a plasticizer is first applied to a peel-off protective film (b) and then dried,

2 - the "adhesive layer (2)/peel-off protective film (b)" set is colaminated on the protective film (a),

3 - the transdermic systems are cut into pastilles with a surface area of between 5 cm^2 and 50 cm^2.

27) Manufacturing process for devices according to claim 12 or 13, characterized in that:

1 - a solution of adhesive layer (2) in heptane loaded with Trimegestone and optionally a plasticizer is first applied on a protective film (a) and then dried,

2 - the "adhesive layer (2)/protective film (a)" set is colaminated on a peel-off protective film (b),

3 - the transdermic systems are cut into pastilles with a surface area of between 5 cm^2 and 50 cm^2.

28) Manufacturing process for devices according to claim 12 or 14, characterized in that:

1 - there are first applied:

a) onto a peel-off protective film (b), a solution of adhesive layer (3) in heptane, and then dried

b) a solution of adhesive layer (2) in heptane loaded with Trimegestone onto a temporary peel-off protective film (b'), then dried,

2 - the "adhesive layer (2) loaded with Trimegestone/temporary peel-off protective film (b')" set is colaminated on the "adhesive layer (3)/peel-off protective film (b) set,

3 - the temporary protective film (b') is peeled away,

4 - the "adhesive layer (2)/adhesive layer (3)/peel-off protective film (b)" set is colaminated onto a protective film (a)

5 - the transdermic systems are cut into pastilles with a surface area of between 5 cm^2 and 50 cm^2.

29) Manufacturing process for devices according to claim 12 or 15, characterized in that

1 -

a) a solution of adhesive layer (1) in heptane is first applied to a temporary peel-off protective film (b') and then dried,

b) a solution of adhesive layer (2) in heptane loaded with Trimegestone is first applied to a temporary peel-off protective film (b'') and then dried,

c) a solution of adhesive layer (3) in heptane is first applied to a peel-off protective film (b) and then dried,

2 - the "adhesive layer (1)/temporary peel-off protective film (b')" set is colaminated onto a protective film (a)

3 - the temporary protective film (b') is peeled away,

4 - the "adhesive layer (2) loaded with Trimegestone/temporary adhesive layer (b'')" set is colaminated on the "adhesive layer (1)/protective film (a)" set,

5 - the temporary protective film (b") is peeled away

6 - in the final colamination operation, the "adhesive layer (3)/peel-off protective film (b)" set is colaminated on the "loaded layer (2)/adhesive layer (1)/protective film (a)" set,

7 - the transdermic systems are cut into pastilles with a surface area of between 5 cm^2 and 50 cm^2.

30) Manufacturing process for the device according to claim 19, characterized in that:

Stage I: for the manufacture of the patch corresponding to compartment (A)

1 - the silicone adhesive polymer layer loaded with Trimegestone and optionally one or more additives is coated on the protective film (a),

2 - the solvent is evaporated off until the "matrix loaded with Trimegestone (I)/protective film (a)" set corresponding to compartment (A) is obtained,

3 - the "matrix loaded with Trimegestone/protective film (a)" set is colaminated on a peel-off protective film (b'),

4 - a patch of 5 to 50 cm^2 is cut out,

Stage II: for the manufacture of the patch corresponding to compartment (B)

1 - the adhesive polymer layer loaded with an oestrogen compound and optionally one or more additives such as a hydrophilic polymer, an absorption promoter or a plasticizer is coated on the protective film (a'),

2 - the solvent is evaporated off until the "matrix loaded with oestrogen/protective film (a')" set corresponding to compartment (B) is obtained,

3 - the "matrix loaded with oestrogen/protective film (a')" set is colaminated onto peel-off protective film (b"),

4 - a patch of 5 to 50 cm^2 is cut out,

Stage III: for the formation of the "bipatch"

1 - the peel-off protective film (b') is peeled from the patch obtained in Stage 1,

2 - the "matrix loaded with Trimegestone/protective film (a)" set is transferred to a peel-off protective film (b),

3 - the peel-off protective film (b'') is peeled from the patch obtained in Stage 2,

4 - the "matrix loaded with oestrogen/protective film (a')" set is transferred to the previous peel-off protective film (b), respecting a distance of 1 to 10 mm or after placing a barrier between compartments (A) and (B).

31) Device according to any one of claims 12 to 16, for use in a delivery process, either of Trimegestone and/or one or more pharmaceutically acceptable derivatives or of Trimegestone combined with an oestrogen, to a patient by application of the matrix/matrices of the device to the skin or to the mucous membranes of said patient.

32) Esters in position 21 of the Trimegestone characterized in that the remainder of the ester contains 1 carbon atom or from 3 to 12 carbon atoms.

ABSTRACT

A subject of the invention is devices intended for transdermic administration characterized in that they contain:

- a protective film (a),
- a single-layer, two-layer or three-layer matrix loaded with Trimegestone and optionally a matrix loaded with oestrogen,
- a peel-off protective film (b),

their preparation process and their use as medicaments.

Figure No.1 : Structure of single-layer patch ($20cm^2$)

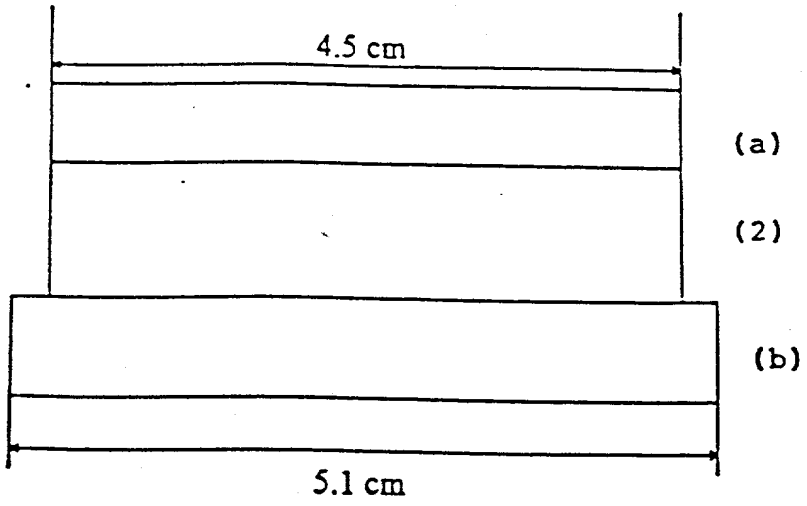

FIGURE 1

REPLACEMENT SHEET (RULE 26)

Figure No.2 : Structure of a two-layer patch ($20cm^2$)

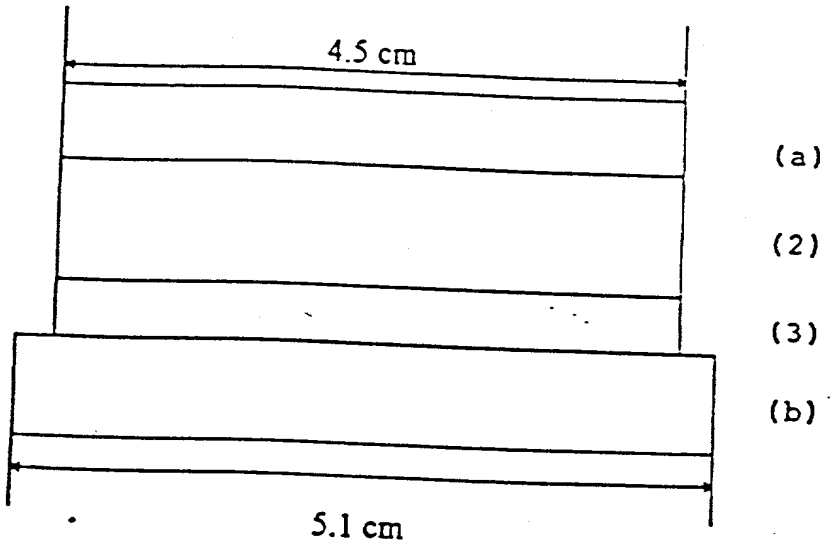

FIGURE 2

REPLACEMENT SHEET (RULE 26)

Figure No.3 : Structure of a three-layer patch ($20cm^2$)

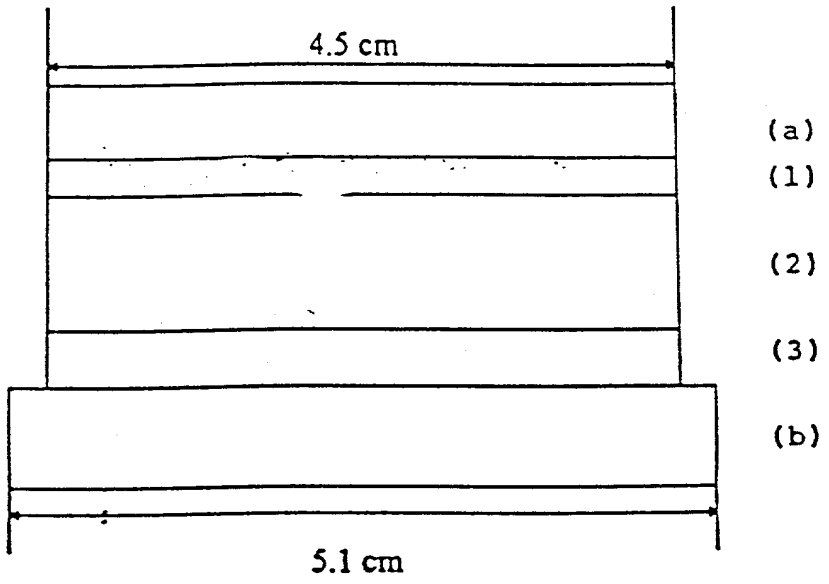

FIGURE 3

REPLACEMENT SHEET (RULE 26)

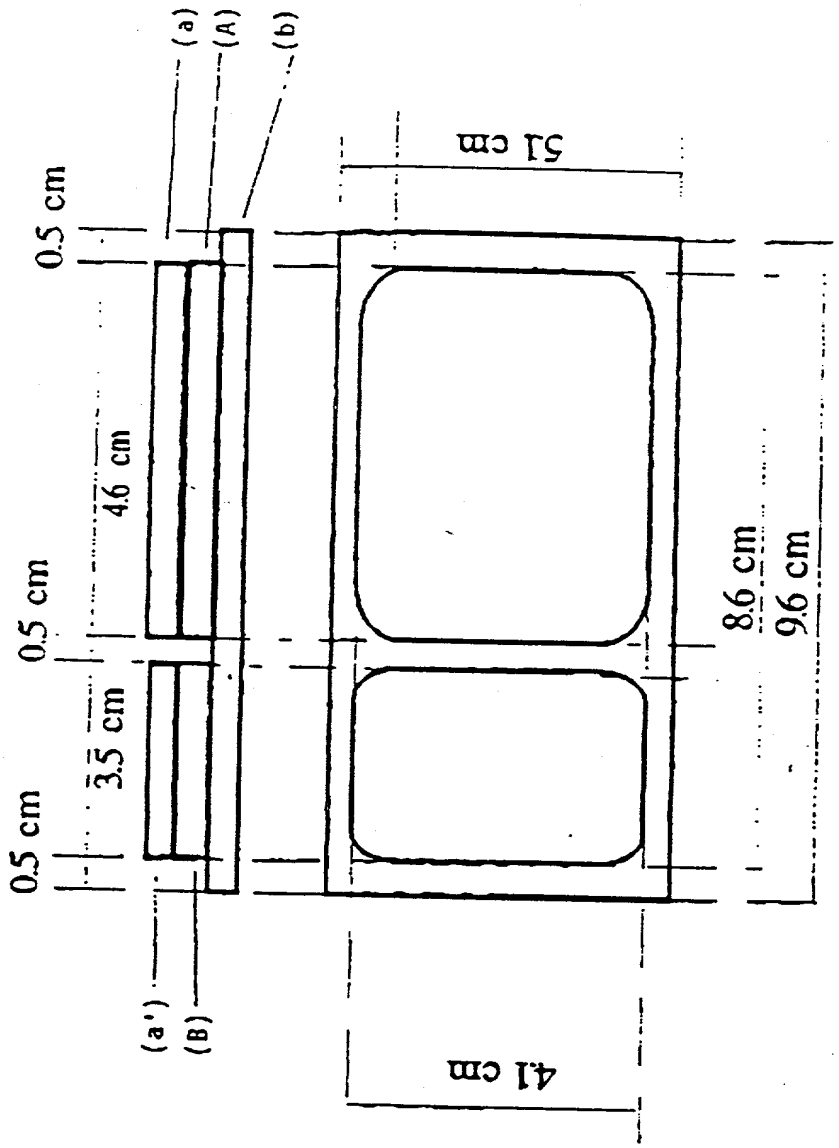

FIGURE 4

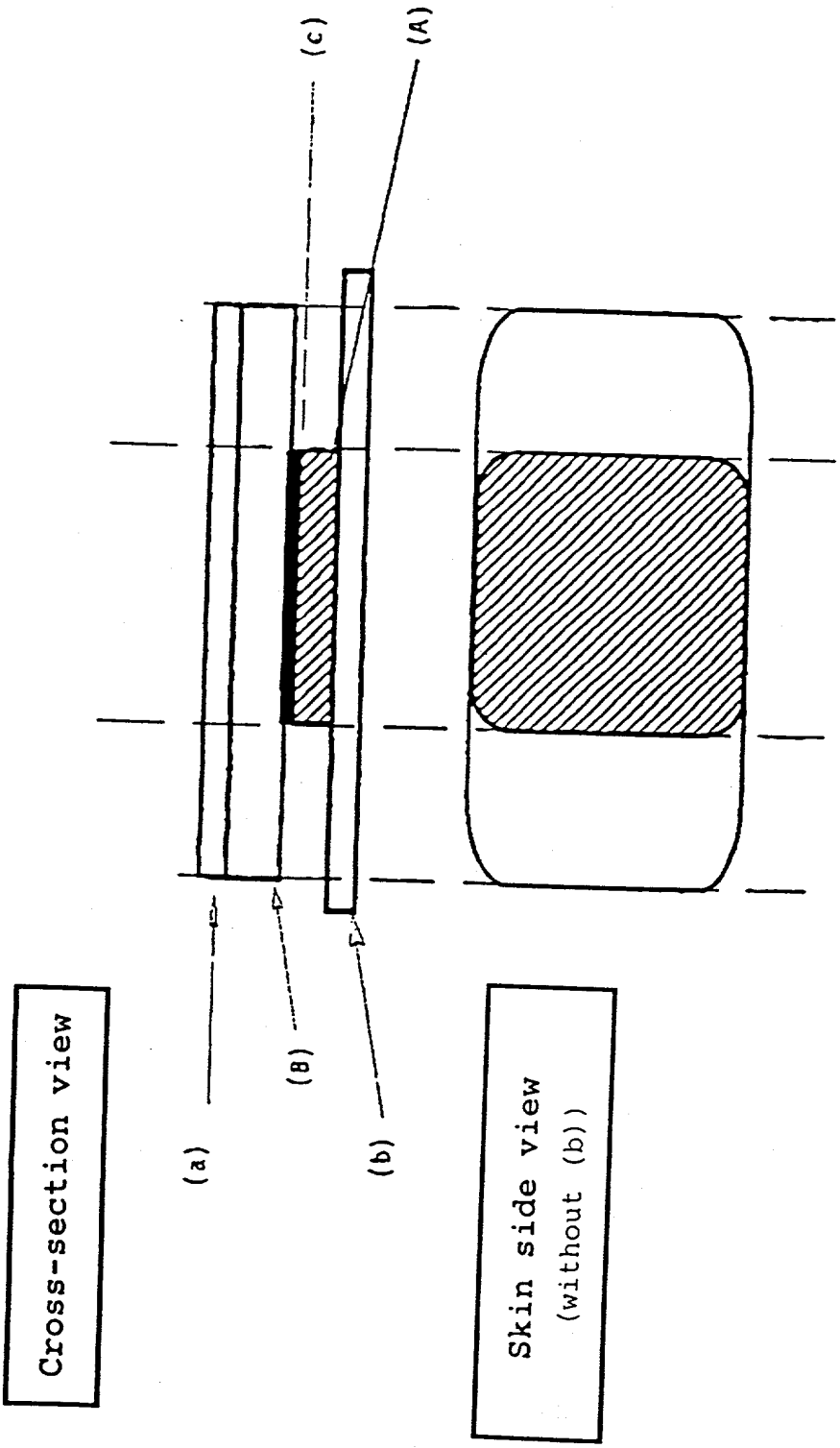

FIGURE 5

146.1307

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: :
JEAN-LUC DUBOIS :
Serial No.: 202,217 :
Filed: December 9, 1998 :
For: NEW DEVICES...AS MEDICAMENTS :

600 Third Avenue
New York N.Y. 10016

DECLARATION

Asst. Commissioner for Patents
Washington, D.C. 20231

Sir:

I hereby declare that:

That Mr. Jean-Luc Dubois formerly residing at 17 rue Anatole France, 91120 Palaiseau, France and now an employee of Sanofi Recherche, 371 rue du Professeur Blayac, 34000 Montpellier, France is the inventor of the subject matter of the invention for which a patent is sought based on United States Patent Application Serial No. 202,217 filed on December 9, 1998 and was filed as PCT International Application No. PCT/FR97/01023 filed June 10, 1997.

That Mr. Dubois has refused to execute the application as can be seen from my declaration filed herewith and I am executing the application on behalf of Hoechst Marion Roussel who owns the application as can be seen from my declaration to avoid loss of the priority rights.

I hereby state that I have reviewed and understand the contents of the above-identified specification and claims, as

amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations §1.56.

I hereby claim foreign priority benefits under Title 35 United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application No. 96/07208, Country: France,
Date: June 11, 1996.

Prior Foreign Application No. PCT/FR97/01023, Country: France
Date: June 10, 1997.

As named inventor, I hereby appoint the following registered practioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the specification or any patent issuing thereon.

Name of First Inventor: Jean-Luc Dubois, c/o Sanofi Recherche, 371 Rue du Professeur Blayac 34000 Montpellier, France.

That I am executing this application on behalf of Hoechst Marion Roussel in my capacity as head of the Patent Department since Jean-Luc Dubois is bound by French law and by his employment contract to assign his inventions to Hoechst Marion Roussel as can be seen from the copy of the French law and employment contracts filed with my declaration as well as English translations thereof.

Hoechst Marion Roussel

Jean Claude Vieillefosse

Jean-Claude Vieillefosse
Head of the Patent Department

Jean-Claude VIEILLEFOSSE
CHEF DU DÉPARTEMENT DES BREVETS
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Date: September 1, 1999

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